REMARKS

Claims 1-3, and 5-20 are pending in the application. Claims 6, 7, 14 and 15 remain withdrawn from consideration.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection of claims 1-3, 5, 8-13, 17 and 20 under 35 U.S.C. §103(a) as being unpatentable over Gryaznov *et al.* (U.S. Patent No. 5,571,903) in view of Agrawal *et al.* (U.S. Patent No. 5,691,316) in view of Applicants' last response "since it is clear that Agrawal *et al.* does not teach the terminal covalent attachment of cyclodextrin to oligonucleotides."

Applicants further gratefully acknowledge the Examiner's apparent withdrawal of the rejection of claims 16-19 under 35 U.S.C. § 112, first paragraph in view of the fact that "it is clear that the compositions of the present invention need only one enabled use to satisfy the requirements of this statute...(and that)...[t]he pharmaceutical compositions of (the) instant claims can be used in a cell for diagnostic purposes, for example." Applicants respectfully note, however, that this portion of the Office Action (at page 2, paragraph 3) appears to be missing the words "is withdrawn" after "rejection of claims 16-19 under 35 USC 112, 1st paragraph" in the first line of this section. Accordingly, Applicants respectfully request confirmation that the rejection of claims 16-19 under 35 U.S.C. § 112, first paragraph has indeed been withdrawn.

The outstanding rejections are addressed below.

Obviousness-Type Double Patenting

Claims 18 and 19 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-22 of U.S. Patent No. 6,372,427 in view of U.S. Patent No. 4,235,871, Papahadjopoulos et al. (1980). Applicants gratefully acknowledge that the previous rejection of claim 18-19 for obviousness-type double patenting in view of the '427 patent alone appears to have been withdrawn in light of Applicants' last Response.

In an effort to expedite prosecution of the application, and not in acquiescence to the rejection, Applicants enclose herewith a terminal disclaimer over U.S. Patent No. 6,372,427. In view of this submission, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 103

Claims 1-3, 5, 8-13, 16-17, and 20 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gryaznov *et al.* (U.S. Patent No. 5,571,903) (the '903 patent) in view of Weber *et al.* (1992). In particular, the Office Action states that "[i]t would have been obvious at the time of the instant invention to substitute one functionally equivalent binding pair for another with the expectation that the prior art binding pair would function in the same manner as those disclosed in Gryaznov *et al.*"

Applicants respectfully traverse this rejection because the Office Action does not present a *prima case* for obviousness based upon the combined teachings of the Gryaznov *et al.* patent and Weber *et al.* reference. In particular, as stated in M.P.E.P. § 2142:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

Applicants respectfully aver that the '903 patent and Weber *et al.* reference do <u>not</u>, individually or combined, teach or suggest all of the limitations of independent claims 1 and 8, or, necessarily, all of the limitations of claims 2, 3, 5, 9-13, 16, 17 and 20, which depend from these claims and therefore share their limitations. In particular, neither the '903 patent nor the Weber *et al.* reference teach an <u>oligonucleotide</u> that is <u>covalently linked</u> to a <u>streptavidin</u> or a

cyclodextin molecule and paired with a second oligonucleotide that is covalently linked to a biotin or adamantane molecule, respectively, as required by both claims 1 and 8.

Independent claim 1 is directed to a composition comprising at least two synthetic oligonucleotides, wherein a first oligonucleotide is covalently linked to a first binding partner and a second oligonucleotide is covalently linked to a second binding partner. The first and second binding partners are selected from the group consisting of cyclodextrin and adamantane, and streptavidin and biotin. Each oligonucleotide comprises a region complementary to a tandem, non-overlapping region of a target nucleic acid, the tandem non-overlapping regions of the target nucleic acid being separated by 0 to 3 bases. The target nucleic acid is an mRNA, a single-stranded viral RNA, or a single-stranded viral DNA.

Independent claim 8 is directed to a dimeric structure comprising a first synthetic oligonucleotide and a second synthetic oligonucleotide, each oligonucleotide comprising a region complementary to one of tandem, non-overlapping regions of a target nucleic acid. The target nucleic acid is an mRNA, a single-stranded viral RNA, or a single-stranded viral DNA. The first oligonucleotide has a first binding partner covalently attached to a 3' terminus. The second oligonucleotide has a second binding partner covalently attached to a 5' terminus. The first and second binding partners are selected from the group consisting of cyclodextrin and adamantane, and biotin and streptavidin. The first and second binding partners are bound as a dimer when the first and second oligonucleotides are hybridized to the target nucleic acid.

The '903 patent teaches the covalent attachment of a number of "terminal binding moieties" to oligonucleotides, but none of these are the claimed cyclodextrin / adamantane and biotin / streptavidin binding pairs, and, further, the teachings of the '903 patent would not have suggested the use of these claimed binding pairs in any event, as described in further detail below. Furthermore, the Weber *et al.* reference teaches a biotin / streptavidin binding pair, but not an *oligonucleotide*, and certainly not a *pair* of oligonucleotides covalently linked to biotin and streptavidin. Therefore, the combined teachings of Weber *et al.* and the '903 patent fail to teach or suggest a first oligonucleotide that is covalently linked to a streptavidin or a cyclodextin molecule and a second oligonucleotide that is covalently linked to a biotin or adamantane

molecule. Accordingly, as the references do not supply every element of the claimed invention, they do not provide support for a *prima facie* case of obviousness of the rejected claims.

Indeed, the examiner previously acknowledged the criticality of this factor in her withdrawal of the rejection under 35 USC §103 in view of the combined teachings of Gryaznov *et al.* (U.S. Patent No. 5,571,903) and Agrawal *et al.* (U.S. Patent No. 5,691,316) in view of Applicants' last response, stating "since it is clear that Agrawal *et al.* does not teach the terminal covalent attachment of cyclodextrin to oligonucleotides."

Even if the combination of the '903 patent and Weber *et al.* did supply every element of the claimed invention, which it doesn't, these teachings still fail to supply the skilled artisan with either a motivation to combine this art, or a reasonable expectation of success in so doing. Applicants specifically disagree with the assertions of the Office Action on this point. In particular, the Office Action opines that it would have been obvious at the time the invention to modify the oligonucleotides of the '903 patent with the streptavidin and biotin complex of Weber *et al.*, because "[t]he terminal binding pairs must also react specifically with each other." In fact, no such assurance of success is provided by the '903 patent, as supplemented by the teachings of Weber *et al.* Applicants respectfully aver that this statement in support of the rejection is an improper overgeneralization, and that the binding behavior of the claimed cyclodextrin / adamantane and biotin / streptavidin binding pairs cannot be predicted from teachings of the '903 patent.

Indeed, the interactions between the cyclodextrin and adamantane binding pair, and between the biotin and streptavidin binding pair are specific, high-affinity, and yet non-covalent, interactions that are not taught by the '903 patent and that cannot reasonably be inferred from its teachings. In particular, the '903 patent teaches moieties that either interact nonspecifically and with low affinity, or that interact specifically only by forming covalent linkages ("Preferably, whenever [the moieties] form a covalent linkage, or bridge, [the moieties] must react specifically with each other when brought into juxtaposition ... ." (at col. 6, lines 51-53)). The '903 patent does not teach or suggest *non-covalently* interacting moieties that *specifically react* with each other. Further, the non-covalent interacting moieties taught by the '903 patent also differ in that they form only nonspecific, low affinity complexes. The nonspecific, low affinity binding pairs

taught by the '903 patent include, for example, paired lipophilic groups (*e.g.* "alkyl groups, fatty acids, fatty alcohols, steroids, waxes, fat-soluble vitamins, and the like"; col. 6, lines 7-8), which interact by relatively nonspecific, and low affinity, hydrophobic interactions.

In contrast, the claimed embodiments require the presence of a pair of high affinity, highly specific non-covalently interacting binding partners (page 14, lines 11-15). The '903 patent does not teach the terminal covalent attachment of streptavidin or biotin to the 3'-end or 5'-end of an oligonucleotide. Nor does the '903 patent teach or suggest that a high-affinity, high-specificity non-covalently interacting binding pair, such as streptavidin/biotin, could be substituted for the specific terminal binding moieties of the '903 patent, which require a formation of a covalent linkage. Accordingly, the '903 patent provides no motivation to modify its teachings, or to otherwise combine its teachings with the Weber *et al.* teachings on the streptavidin / biotin binding pair, to arrive at the claimed invention.

Furthermore, the Weber *et al.* reference does not provide such a motivation either. Indeed, Weber *et al.* merely investigates the differing thermodynamic and crystallographic binding characteristics of streptavidin/biotin and streptavidin-HABA (2-(4'-hydroxyphenylazo)-benzoic acid) to better understand the principles of protein-ligand interactions applicable to rational drug design (see page 3197, Introduction, of Weber *et al.*). Applicants respectfully note that Weber *et al.* is devoid of any motivation to covalently attach streptavidin or biotin to other molecular entities. Further, Weber *et al.* notes streptavidin also binds to other compounds, which differ structurally from biotin (see page 3197, Introduction, of Weber *et al.*). This *teaches away* from the use of streptavidin as an ideal binding partner where predictability and specificity of interaction is desired. Weber *et al.* does not teach or suggest the terminal covalent attachment of streptavidin or biotin to another molecular entity in general, let alone to the 3'-end or 5'-end of an oligonucleotide, in particular. Neither does Weber *et al.* in any way provide a motivation to combine its teachings with the art of oligonucleotides in general, or the teachings of the '903 patent, in particular. Accordingly, further in view of the fact that there would have been no motivation to combine the teachings of the '903 patent with the teachings of Weber *et al.*, a proper *prima facie* obviousness rejection has not been established.

Still further, the '903 patent contains no reasonable expectation of success in combining the teachings of the '903 patent with the teachings of Weber *et al.* because there was no indication of a functional equivalency between the inherently low affinity, non-specific, non-covalent binding characteristics taught by the '903 patent and the high-affinity, highly specific, non-covalent interaction characteristics of streptavidin and biotin disclosed in Weber *et al.* Neither was there any indication of a functional equivalency between the specifically-reacting covalent linking pairs taught by the '903 patent and the high-affinity, highly specific non-covalent interaction characteristics of streptavidin and biotin disclosed in Weber *et al.* Accordingly, there would have been no reasonable expectation of success of combining these references to arrive at streptavidin/biotin-coupled oligonucleotide pairs as argued by the Examiner. This is so because there was no indication in the art that either the improved hybridization of the oligonucleotide pairs taught by the '903 patent or the unique binding characteristics of streptavidin and biotin, as taught in Weber *et al.*, would be maintained if the distinct compositions taught by each were combined and appropriately substituted. Thus, a reasonable expectation of success in combining the teaching of the '903 patent and Weber *et al.* is lacking. Accordingly, a *prima facie* case for obviousness has not been presented.

In view of the above-detailed insufficiencies in the combined teachings of the '903 patent and Weber *et al.*, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §103(a).

CONCLUSION

In view of the arguments set forth above, Applicants respectfully request reconsideration and reexamination of the above-referenced patent application. Applicants submit that the rejections contained in the Office Action mailed on August 24, 2005, have been overcome, and that the claims are in condition for allowance.

If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

This response under 37 C.F.R. §1.111 is being submitted within three months of the mailing date of the Office Action, and, accordingly, no other fees are believed to be due in connection with this response. However, please charge any fees dues or refund any overpayment to Deposit Account No. 08-0219.

Respectfully submitted,

Date: Nov. 10, 2005

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